REMARKS/ARGUMENTS

Claims 40, 42-43, 46-49 and 60-61 have been resubmitted.

35 U.S.C. §103

Claims 40, 42-43, 46-49 and 60-61 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Sawhney et al. (U.S. Patent No. 5,570,708) in view of Hubbell et al. (U.S. Patent No. 5,410,016), Thompson et al. (U.S. Patent No. 6,683,064) and Hai et al. (Bioconjugate Chem., 2000). Applicants submit that the present invention is not *prima facie* obvious over the Sawhney, Hubbell or Thompson patents or the Hai reference, either alone or in combination. Applicants therefore respectfully traverse and request reconsideration.

A. The prior art does not teach or suggest a polymeric primer for integrating a hydrogel to muscoskeletal tissue, as claimed in claim 40:

40. (Previously Presented) A method of integrating a hydrogel to a musculoskeletal tissue, comprising the steps of:

(a) priming the surface of a musculoskeletal tissue by treating the musculoskeletal tissue with a priming agent to create a primed musculoskeletal tissue, wherein the priming agent comprises ***a polysaccharide with at least one aldehyde group and a first at least one free radical polymerizable group, and the at least one aldehyde group reacts with the musculoskeletal tissue to covalently bind the musculoskeletal tissue and the priming agent;***

(b) adding to the primed musculoskeletal tissue a polymerizable agent and a radical photoinitiator, wherein the polymerizable agent comprises a

biocompatible polymer having a second at least one free radical polymerizable group; ***and***

(c) reacting the primed musculoskeletal tissue and the polymerizable agent by a radical reaction to create an integrated hydrogel covalently bound to the musculoskeletal tissue, (emphasis added)

The present claimed invention is directed toward a method of integrating a hydrogel to a musculoskeletal tissue where the hydrogel is covalently bound to the tissue through a priming agent. The priming agent comprises a *polysaccharide with at least one aldehyde group* ***and*** *a first at least one free radical polymerizable group.* The aldehyde group reacts with the musculoskeletal tissue to covalently bind the polysaccharide to the musculoskeletal tissue. After applying the polysaccharide primer to the tissue, a polymerizable agent and a radical photoinitiator are added to the primed tissue where the polymerizable agent has at least one free-radical polymerizable group. A radical reaction is then initiated, creating a hydrogel from the polymerizable agent and where the polymerizable agent is also covalently bound to the polysaccharide primer, allowing for an integrated hydrogel covalently bound to the musculoskeletal tissue *through the polysaccharide.* See Figure 7 of the present specification.

In contrast, none of the prior art cited in the rejection of the claims teaches or suggests *a large molecule polymeric primer that covalently attaches to the tissue.* The Sawhney patent teaches priming a tissue surface with a polymerization initiator. The initiator is applied to a surface to form an absorbed layer, providing an "activated tissue surface." See column 5, line 43 to column 6, line 27. Sawhney suggests that a monomer can be optionally included in the priming step. A polymerizable agent and initiator are then added to the primed tissue and polymerization is allowed to take place. It is important to note that

the primer of the Sawhney patent does not *covalently* link any monomers or subsequently formed hydrogel to the surface. The functional groups of the monomers of the Sawhney patent are chosen to crosslink to each other to form polymerized hydrogel layers, not to covalently bond to the host tissue, and as a result the bonding of the hydrogel is purely mechanical interlock, as described by Sawhney as "highly adherent" (abstract) or "strong adhesion" (col 3 lines 23-24).

Neither the Hubbell and Thompson patents nor the Hai reference teach priming a tissue surface with a functionalized polysaccharide to integrate a hydrogel to the tissue surface. The Hubbell patent teaches hydrogels of polymerized and crosslinked macromers where the macromers comprise hydrophilic oligomers having biodegradable regions and end regions capable of polymerization or crosslinking by free radical polymerization. The Hubbell patent describes hydrogels for controlled drug delivery, adhesion prevention, or as a tissue sealant; there is no teaching or suggestion of covalent binding of the hydrogels to tissue. The Thompson patent teaches the *in vitro* preparation of a biodegradable carrier by opening sugar rings on a first polysaccharide to form aldehyde groups where the aldehyde groups then form covalent imine crosslinks with a second polysaccharide amine derivative at the amine sites. See the abstract. The Thompson patent teaches a combination of specifically functionalized polysaccharides that react with each other to form crosslinked hydrogels for the delivery of therapeutic agents. The Thompson patent does not teach or suggest covalent binding of the hydrogels to tissue. Finally, the Hai reference teaches altering the pharmacokinetics of a potentially therapeutic protein by increasing the overall negative charge of purified human hemoglobin by attaching a truncate and modified chondrotin-4-sulfate to the hemoglobin through an aldehyde group on the chondrotin-4-sulfate. The Hai reference does not teach use of a functionalized polysaccharide to prime the surface of tissue

preparatory to integration of a hydrogel. Therefore neither the Sawhney, the Hubbell, nor Thompson patents nor the Hai reference are examples of the use of a functionalized polysaccharide to covalently bind a hydrogel to the surface of a tissue.

The Examiner believes that the skilled artisan in reading the above cited prior art would be motivated to replace the polymerization initiator or the monomer of Sawhney patent with the polysaccharide with aldehyde groups of the Thompson patent and free radical polymerizable groups of the Hubbell patent because the Examiner argues that it is known from the Hai reference that the aldehyde groups can bind to proteins. The Applicants submit that this is not an obvious combination because the monomer of the Sawhney reference, which is optional, is not functional without the polymerization initiator that is used to prime the tissue. Sawhney does not teach or suggest that the monomer is involved in the priming of the surface and the subsequent adherence of the hydrogel to the tissue surface. Nor does the Sawhney patent teach or suggest that the monomer can be used in place of the polymerization initiator in the initiation system.

The Examiner believes that one of ordinary skill in the art would have been motivated to specifically choose chondroitin sulfate with at least an aldehyde group because the Hai reference teaches that this polysaccharide has the potential to alter the *in vivo* properties of the proteins, possibly increasing their therapeutic utility. Applicants respectfully disagree. The method of the present invention is for integrating a hydrogel to a musculoskeletal tissue, not to alter the properties of any proteins or to render any therapeutic utility beyond acting as a scaffold for subsequent regeneration of musculoskeletal tissue. Therefore, the fact that the chondroitin sulfate of the Hai reference may be

therapeutically advantageous would not be a motivation to use it in place of the polymerization initiator or the monomer of the Sawhney patent.

Furthermore, the Examiner believes that there was a reasonable expectation of success using the chondroitin sulfate of the Hai reference because the Thompson patent teaches that chondroitin sulfate with aldehyde groups is beneficial for use in repair of cartilage tissue. Applicants would like to point out that the chondroitin sulfate with aldehyde groups of the Thompson patent is used to form a gel or sponge-like carrier for therapeutic agents including biological factors that are useful for cartilage repair. It is not the chondroitin sulfate itself that is beneficial, but the therapeutic molecules that are being delivered by the carrier made up of chondroitin sulfate. Thompson does not teach or suggest the treatment or repair of tissue or cartilage with polysaccharide hydrogels alone.

B. The prior art does not teach the use of a polysaccharide or polymer having heterofunctional polymerizable groups, as described in the claim 40:.

40. (Previously Presented) A method of integrating a hydrogel to a musculoskeletal tissue, comprising the steps of:

(a) priming the surface of a musculoskeletal tissue by treating the musculoskeletal tissue with a priming agent to create a primed musculoskeletal tissue, wherein the priming agent comprises ***a polysaccharide with at least one aldehyde group and a first at least one free radical polymerizable group,*** and the at least one aldehyde group reacts with the musculoskeletal tissue to covalently bind the musculoskeletal tissue and the priming agent. (emphasis added)

As described above, the present claimed invention is directed toward a method of integrating a hydrogel to a musculoskeletal tissue where the hydrogel is covalently bound to the tissue through a heterofunctionalized polysaccharide priming agent. The aldehyde functional group reacts with the musculoskeletal tissue to covalently crosslinks (or polymerizes) the polysaccharide to the musculoskeletal tissue while the free-radical polymerizable group reacts with polymerizable agent by a radical reaction to form an integrated hydrogel covalently bound to the musculoskeletal tissue *through the polysaccharide.* See Figure 7 of the present specification. It is the presence of the heterfunctional polymerizable or crosslinking groups that allows for the novel function of the polysaccharide as a priming agent for integrating a hydrogel to the musculoskeletal tissue.

The Examiner believes that it would be obvious to use a heterofunctional polysaccharide to replace the monomer of the Sawhney patent to give the present invention because the Sawhney patent teaches that at least two polymerizable groups are preferable and that although acrylate is the preferred polymerizable group, other polymerizable groups may be used with acrylates, including aldehydes. Applicants respectfully disagree with this interpretation of the Sawhney patent. The Sawhney patent teaches a bifunctional or polyfunctional monomer, *but not a heterofunctional monomer.* The Sawhney patent is stating the obvious when teaching that at least two polymerizable groups are required for function becausein order for the monomer to form a crosslinked hydrogel there must be at the very least two functional groups per monomer. If there were only one, then a crosslinked network cannot be formed. The Sawhney patent in describing the "at least two polymerizable groups" *is not describing* a heterofunctional monomer in which one group reacts with one target (tissue) and the other functional group of a different chemistry reacts with a different target (hydrogel) such as in the present invention.

In the Sawhney patent, the preferred reactive groups are free radical polymerizable groups. The Sawhney patent also suggests other polymerization chemistries in which the different functional groups *react with each other*, such as amines or thiols with aldehydes. The Sawhney patent also lists various polymerization chemistries such as amines or thiols *reacting with* aldehydes (col 8 lines 44-49) and states that the reactants may be both covalently attached to a single macromer. However, this is still describing a system of functional groups that react together. The Sawhney patent does not suggest a heterofunctional polymer in which the functional groups have different chemistries and are not meant to react with each other. By contrast, in the present invention, the heterofunctional groups on the polysaccharide interact with different targets: the aldehyde reacts with host tissue and the free-radical polymerizable group reacts with the free radical polymerizable hydrogel.

Additionally, the Hubbell and Thompson patents and the Hai reference disclose and teach only macromers or polysaccharides that are basically homofunctional with respect to the chemistry of the polymerizable or crosslinking group, although they may have more than one group per monomer or macromer (i.e. bifunctional or multifunctional). The polymerizable regions of the macromers of the Hubbell patent may be polymerizable by free radical generation or by "other chemistries such as water and amine initiation schemes with isocyanate or isothiocyanate- containing macromers." See column 9, lines 6-18. The Thompson patent teaches a polysaccharide with an aldehyde group is reacted with a second polysaccharide with an amine group and the Hai reference only discloses truncated chondroitin sulfate having an aldehyde group that reacts with free amines in proteins. Again, these are describing a system of functional groups that react together to form hydrogels or modified purified proteins, they are not describing a heterofunctionalized polymer in which the

functional groups react with different target molecules. Therefore, the polymers of the Sawhney, Hubbell and Thompson patents or the Hai reference cannot function in the same way as the functionalized polysaccharide priming agent of the present invention.

Nor would it have been obvious to the skilled artisan, without having the present invention as a guide, to select the free radical polymerizable groups of the Hubbell and Sawhney patents and the aldehyde group of the Thompson patent and Hai reference. The Sawhney, Hubbell and Thompson patents teach the crosslinking of the monomers, macromers or polysaccharides to form a hydrogel. The polymerizable groups on the monomers, macromers, or polysaccharides were chosen for maximum intermolecular crosslinking between like molecules and not two distinct surfaces. To have a heterofunctional molecule would decrease the strength of the crossl-linking. Therefore, there would be no motivation to have a heterofunctional molecule with respect to polymerizable groups as it would render the methods of the prior art less effective.

Applicants submit that the skilled artisan, upon reading the Sawhney, Hubbell and Thompson patents and the Hai reference would not be motivated to substitute the polymerization initiator or monomer of the Sawhney patent with the polysaccharide with aldehyde groups of the Thompson patent or the chondrotin-4-sulfate of the Hai reference. The prior art does not teach or suggest the use of heterofunctionalized groups on polysaccharides, monomers, or macromers, in which one type of functional group covalently binds to a tissue target and the second functional group *on the same molecule* participates in a free radical polymerization with a polymerizing hydrogel, thus providing a covalent integration of a hydrogel to a musculoskeletal tissue.

Applicants thus respectfully request withdrawal of the rejection.

Double Patenting

Claims 40, 42-43, 46-49 and 60-61 have been provisionally rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 40-75 of copending Application No. 11/369,578, claims 1, 2, 9,10 and 15copending Application No. 10/962,278 in view of the Hai reference, claims 4-7, 15, 18 and 22 of copending Application No. 11/637,516 in view of the Hai reference or claims 53, 63, 65 and 77 of copending Application No. 10/681,753 in view of the Hai reference.

Applicants acknowledge the rejection and will address the rejection when claims are allowed in either the present case or any of the copending applications.

CONCLUSION

Applicants submit that the claims stand ready for allowance and such allowance is courteously solicited.

In the event the Examiner wishes to discuss any aspect of this response, please contact the attorney at the telephone number identified below.

☒ The Commissioner is hereby authorized to charge payment of the following fees with this communication or credit any overpayment to Deposit Account No. 02-3223:

☒ Any filing fees under 37 CFR 1.16 for the presentation of extra claims.

Respectfully submitted,

By: Barbara S. Gibbs

Barbara S. Gibbs, Ph.D.
Attorney Registration No. 44,708